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Applicant: Smith, K. A.

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Search Strategy

Stedman's Medical Dictionary 27th Edition

potentiation: Interaction between two or more drugs or agents resulting in a pharmacologic response greater than the sum of individual responses to each drug or agent.

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FILE 'USPATFULL' ENTERED AT 17:31:04 ON 11 DEC 2002

E SMITH KENDALL A/IN

L1 12 S E3
L2 11363 S (IL-2 OR INTERLEUKIN-2)
L3 5911 S L2 AND (ANTIVIRAL OR ADJUVANT OR IMMUNE POTENTIAT?)
L4 2265 S L3 AND ANTIVIRAL?
L5 1521 S L4 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L6 198 S L4 AND (IL-2/CLM OR INTERLEUKIN-2/CLM)
L7 107 S L6 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L8 47 S L7 AND (HIV/CLM OR HUMAN IMMUNODEFICIENCY VIRUS/CLM)
L9 30 S L6 AND (HCV OR HEPATITIS C VIRUS)
L10 12 S L9 AND (HCV/CLM OR HEPATATIS/CLM)

FILE 'MEDLINE' ENTERED AT 18:09:09 ON 11 DEC 2002

E SMITH K A/AU

L11 305 S E3-E5
L12 84 S L11 AND (IL-2 OR INTERLEUKIN-2)
L13 44911 S (IL-2 OR INTERLEUKIN-2)
L14 44827 S L13 NOT L11
L15 673 S L14 AND (IMMUNE POTENTIATION OR IMMUNOPOTENTATION OR POTENTIA
L16 67 S L15 AND (VIR?)
L17 221 S L15 AND (IL-2/TI OR INTERLEUKIN-2/TI)
L18 210 S L17 NOT L16

L1 ANSWER 3 OF 12 USPATFULL

2000:40633 Method of stimulation of immune response with low doses of IL-2.

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Cornell Research Foundation, Inc., Ithaca, NY, United States (U.S.
corporation)

US 6045788 20000404

APPLICATION: US 1996-608516 19960228 (8)

DOCUMENT TYPE: Utility; Granted.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of activating the immune system of a subject comprises the chronic administration of low doses of an agent such as IL-2, fusion proteins thereof and derivatives thereof that are pharmaceutically acceptable. The agent is provided as a dermal composition, transdermal delivery device and electrotransport device as well as in the form of a kit for self-administration.

CLM What is claimed is:
1. A method of chronic stimulation and/or maintenance of immune response, comprising the administration or application or self-application to a subject or the subject's self-administration of a composition comprising an agent selected from the group consisting of natural and recombinant IL-2, pharmaceutically-acceptable fusion proteins of natural and recombinant IL-2, PEG-natural and -recombinant IL-2, lipid-conjugated natural and recombinant IL-2, therapeutic agent-linked natural and recombinant IL-2, reduced natural and recombinant IL-2, glycosylated natural and recombinant IL-2, non-glycosylated natural and recombinant IL-2, and mixtures thereof, for a period greater than three months in an amount and under conditions effective to release about 100,000 to about 500,000 IU IL2/m.sup.2 body surface/day or equivalent to about 1,000 to about 500,000 IU IL-2/m.sup.2 body surface/day, the agent having a specific activity or 15.times.10.sup.6 IU/mg protein.

2. The method of claim 1, wherein the composition is administered, applied, self-administered, or self-applied by subcutaneous, intramuscular, intradermal, intralymphatic, intratumor, transdermal, intracavitary, transbuccal, transpulmonary, oral, intranasal, transmucosal, intravaginal, intraanal, intrabuccal, or sublingual administration or application, by inhalation, or by implant.

3. The method of claim 1, wherein the composition is self-administered.

4. The method of claim 1, wherein the composition comprises a controlled release composition.

5. The method of claim 1, further comprising adjusting the amount of the agent administered, applied, self-administered, or self-applied by monitoring the blood concentration of the agent, the % saturation of the high affinity IL-2 receptors, or the blood count of at least a cell type selected from the group consisting of circulating lymphocytes, monocytes, and polymorphonuclear leukocytes.

6. The method of claim 1, wherein the subject is a normal subject or a subject afflicted with a condition associated with a viral, bacterial, fungal, and parasitic microorganism, a congenital or acquired immunodeficiency, or a malignancy.

7. The method of claim 6, wherein the subject is HIV seropositive human; and the composition is administered applied, self-administered, or self-applied in an amount and under conditions which substantially avoid increasing the count of circulating microorganisms.

8. The method of claim 1, wherein the subject is an animal.
9. The method of claim 8, wherein the animal is a human.
10. The method of claim 1, wherein the amount of the agent administered, allied, self-administered, or self-applied is effective to elevate the count of at least one blood cell type selected from the group consisting of circulating lymphocytes, monocytes, pa polymorphonuclear leukocytes.
11. The method of claim 10, wherein the amount of the agent administered, applied, self-administered, or self-applied is effective to elevate the count of at least one blond cell selected from the group consisting of circulating T-cells, B-cells, NK cells, monocytes, eosinophils, neutrophils, basophils and antigen-presenting cells.
12. The method of claim 1, wherein the administered, applied, self-administered or self-applied composition is in the form of a powder, a tablet, a capsule, a dragee, a cream, a solution, a suspension, an emulsion, a gel, a spray, a liposome or other micelle, or combinations or mixtures thereof, and formulated prior to administration, application, self-administration or self-application.
13. The method of claim 1, wherein the administered or self-applied composition is in solid form, and formulated prior to administration, application, self-administration, or self-application.
14. The method of claim 13, wherein the administered, applied self-administered or self-applied composition is in lyophilized form.
15. The method of claim 1, wherein the administered, applied, self-administered or self-applied composition is in liquid form.
16. The method of claim 1, wherein the composition is administered, applied, self-administered, or self-applied by means of an inhalant.
17. The method of claim 1, wherein the agent is administered, applied, self-administered, or self-applied as a topical composition, further comprising a carrier or diluent for the agent suitable for topical delivery and an ingredient selected from the group consisting of buffers, salt forming acids and bases, perfumes, colorants, emollients, adjuvants, single or multiple enteric coatings, copolymers, microporous or semi-permeable membranes, enzyme inhibitors, mucoadhesives, chelating agents, particulate systems, viral envelope proteins, liposomes and other micelles, emulsifiers, lipoproteins and other fatty acid derivatives, surfactants, bile salts, hydrophilic, neutral, and hydrophobic polymers and co-polymers, hydrogels, biodegradable polymers and co-polymers, and an additional bioactive agent selected from the group consisting of additional lymphokines or cytokines , and fusion proteins of the lymphokines or cytokines, anti-inflammatories, anti-bacterial, anti-viral, anti-fungal, anti-parasitic, anti-metabolic, anti-inflammatory, vasoactive, anti-neoplastic, bronchodilating, local anesthetic, immunomodulating, growth promoting and regenerating agents, enzymatic, hormonal agents, neurotransmitters, and cell receptor proteins and ligands.
18. The method of claim 17, wherein the composition is in the form of a cream, an ointment, a solution, a gel, a powder, a suspension, an emulsion, encapsulated particles or mixtures thereof.
19. The method of claim 17, wherein the agent is present in an amount of

about 0.0001 to 50 wt % of the composition.

20. The method of claim 17, wherein the composition comprises a controlled release composition.

21. The method of claim 17, wherein the composition is administered by a transdermal delivery device comprising, in a sterile container, a solid support; and a compartment provided in the solid support, the compartment comprising a solution or suspension of the composition, and having one side permeable thereto; whereby when the permeable side of the compartment is placed in contact with an area of a subject's dermis a desired amount of the agent passes from the device onto, and through, the dermis of the subject, over a pre-determined period of time.

22. The method of claim 21, wherein the device comprises a unit dose of the agent.

23. The method of claim 21, wherein the device further comprises a cover placed on the permeable side of the container; the cover being substantially impermeable to the solution or suspension and removable prior to administration, application, or self-application.

24. The method of claim 21, wherein the device is an electrotransport device, further provided with donor and counter electrodes; external power source and control circuitry; wherein the solution or suspension further comprises electroconducting agents, and when the permeable side of the device is placed in contact with an area of the subject's dermis and an electric field is applied to the electrodes, a desired amount of the agent passes from the device onto, and through, the dermis of the subject, over a pre-determined period of time.

25. The method of claim 21, wherein the device is an ultrasound device, further provided with ultrasound transducer, external power source and control circuitry; wherein when the permeable side of the device is placed in contact with an area of the subject's dermis and an electric field is applied to the ultrasound generator, a desired amount of the agent passes from the device onto, and through, the dermis of the subject, over a pre-determined period of time.

26. The method of claim 20, wherein the agent is released by an implant, the implant comprising an amount effective to release the desired amount of the agent over a predetermined period of time.

27. The method of claim 1, further comprising administering or applying to the subject or having the subject self-administer or self-apply a bioactive agent selected from the group consisting of additional lymphokines or cytokines, fusion proteins of the lymphokines or cytokines, anti-inflammatory, anti-bacterial, anti-viral, anti-fungal, anti-parasitic, anti-metabolic, vasoactive, anti-neoplastic, bronchodilating, local anesthetic, immunomodulating, growth promoting, regenerating, enzymatic and hormonal agents, neurotransmitters, and cell receptor proteins and ligands.

28. The method of claim 27, wherein the subject is administered, applied, self-administered, or self-applied the agent and a bioactive agent selected from the group consisting of anti-bacterial agents, anti-fungal agents, anti-parasitic agents and anti-viral agents.

29. The method of claim 28, wherein the bioactive agent comprises one or more anti-viral agents.

30. The method of claim 29, wherein the anti-viral agents are selected from the group consisting of nucleotide analogues and protease inhibitors.

31. The method of claim 30, wherein the subject is administered, applied, self-administers or self-applies, one or more anti-viral agents selected from the group consisting of zidovudine (AZT), 2',3'-dideoxyinosine (ddI), 3'-azido- 2', 3'-dideoxythymidine, d4T, acyclovir, 1,3-dihydro-2-propoxy-methyquanine (gancyclovir), ribavirin, dideoxycytidine (ddC), lamivudine (3TC), and enzyme inhibitors.

32. The method of claim 31, wherein the subject is administered or applied, self-administers or self-applies one or more enzyme inhibitors, and the enzyme inhibitors comprise protease inhibitors.

33. The method of claim 32, wherein the protease inhibitors are saquinovir or invirase.

34. The method of claim 31, wherein the subject is administered or applied, self-administers or self-applies one or more anti-viral agents, and the anti-viral agents are selected from the group consisting of zidovudine (AZT), lamivudine (3TC), d4T, invirase and combinations and mixtures thereof.

35. The method of claim 34, wherein the anti-vital agent combinations administered, applied, self-administered or self-applied comprise zidovudine (AZT), lamivudine (3TC), and d4T, or zidovudine (AZT), lamivudine (3TC), and invirase.

36. The method of claim 35, wherein the anti-viral agent combination administered, applied, self-administered or self-applied comprises zidovudine (AZT), lamivudine (3TC), and d4T, and zidovudine is administered, applied, self-administered or self-applied at about 600 mg/day, lamivudine (3TC) at about 300 mg/day, and invirase at about 600 mg/day.

37. The method of claim 28, wherein the subject is administered, applied, self-administers or self-applies one or more bioactive agents.

38. The method of claim 37, wherein the bioactive agents comprise anti-bacterial agents.

39. The method of claim 37, wherein the anti-bacterial agents comprise antibiotics.

40. The method of claim 39, wherein the antibiotics are selected from the group consisting of pentamidines, trimethoprim-sulfamethoxazole, sulfonamides, penicillins, cephalosporins, aminoglycosides, tetracyclines, chloramphenicols, and combinations and mixtures thereof.

41. The method of claim 37, wherein the bioactive agents comprise anti-fungal agents.

42. The method of claim 41, wherein the anti-fungal agents are selected from the group consisting of flucytosine, amphotericin B, fluconazole, griseofulvine, and combinations and mixtures thereof.

43. The method of claim 37, wherein the bioactive agents comprise anti-parasitic agents.

44. The method of claim 43, wherein the anti-parasitic agents are

selected from the group consisting of pyrimethamine, quinacrine, thiabendazole, levamisol, and combinations and mixtures thereof.

45. The method of claim 37, wherein the bioactive agents comprise anti-metabolic agents.

46. The method of claim 45, wherein the anti-metabolic agents are selected from the group consisting of purine analogues, folic acid analogues, pyrimidine analogues, and combinations and mixtures thereof.

47. A method of chronic stimulation and/or maintenance of immune response, comprising the administration or application to a subject in need of treatment or the subject's self-administration, or self-application of an agent selected from the group consisting of natural and recombinant IL-2, pharmaceutically-acceptable fusion proteins of natural or recombinant IL-2, PEG-natural and recombinant IL-2, lipid-conjugated natural and recombinant IL-2, therapeutic agent-linked natural and recombinant IL-2, reduced natural and recombinant IL-2, glycosylated natural and recombinant IL-2, non-glycosylated natural and recombinant IL-2, and mixtures thereof, for a period greater than three months in an amount and under conditions effective to release about 100,000 to about 500,000 IU IL-2/m.sup.2 body surface/day or equivalent to about 100,000 to about 500,000 IU IL-2/m.sup.2 body surface/day, the agent having a specific activity of 15.times.10.sup.6 IU/mg protein.

48. A method of increasing and/or maintaining the count of circulating blood cells selected from the group consisting of lymphocytes, monocytes, and polymorphonuclear leukocytes, comprising the administration or application to a subject or the subject's self-administration, or self-application of a composition comprising an agent selected from the group consisting of natural and recombinant IL-2, pharmaceutically acceptable Fusion proteins of natural and recombinant IL-2, PEG-IL-2 natural and recombinant, lipid-conjugated natural and recombinant IL-2, therapeutic agent-linked natural and recombinant IL-2, reduced natural and recombinant IL-2, glycosylated natural and recombinant IL-2, non-glycosylated natural and recombinant IL-2, and mixtures thereof, for a period greater than three months in an amount and under conditions effective to release about 100,000 to about 500,000 IU IL-2/m.sup.2 body surface/day or equivalent to about 100,000 to about 500,000 IU IL-2/m.sup.2 body surface/day, the agent having a specific activity of 15.times.10.sup.6 IU/mg protein.

49. The method of claim 48, wherein the composition further comprises an ingredient selected from the group consisting of carriers, diluents, buffers, salt forming acids and bases, perfumes, colorants, emollients, adjuvants, single or multiple enteric coatings, copolymers, microporous or semi-permeable membranes, enzyme inhibitors, mucoadhesives, chelating agents, particulate systems, viral envelope proteins, liposomes and other micelles, emulsifiers, lipoproteins and other fatty acid derivatives, surfactants, bile salts, hydrophilic, neutral, and hydrophobic polymers and co-polymers, hydrogels, biodegradable polymers and co-polymers, and anti-inflammatories, an additional bioactive agent selected from the group consisting of additional lymphokines or cytokines, and fusion proteins of the lymphokines or cytokines, anti-inflammatories, anti-bacterial, anti-viral, anti-fungal, anti-parasitic, anti-metabolic, anti-inflammatory, vasoactive, anti-neoplastic, bronchodilating, local anesthetic, immunomodulating, growth promoting and regenerating agents, enzymatic, hormonal agents, neurotransmitters, and cell receptor proteins and ligands.

50. The method of claim 48, wherein the subject is selected from the group consisting of normal subjects and subjects afflicted with a condition associated with a viral, bacterial, fungal, and parasitic microorganism, a congenital and acquired immunodeficiency, and a malignancy.

51. The method of claim 50, wherein the subject is an HIV seropositive human, and the agent is administered, applied, self-administered, or self-applied in an amount and under conditions which avoid increasing the count of circulating microorganisms.

52. A method of administering or applying to a subject an agent selected from the group consisting of natural and recombinant IL-2, pharmaceutically acceptable fusion proteins of natural and recombinant IL-2, PEG-IL-2 natural and recombinant, lipid-conjugated natural and recombinant IL-2, therapeutic agent-linked natural and recombinant IL-2, reduced natural and recombinant IL-2, glycosylated natural and recombinant IL-2, non-glycosylated natural and recombinant IL-2, and mixtures thereof in the absence of toxicity grade 1 or higher, comprising the administration, application, self-administration, or self-application for a period greater than three months of a composition comprising the agent in an amount and under conditions effective to release about 100,000 to about 500,000 IU IL-2/m.^{sup.2} body surface/day or equivalent to about 100,000 to about 500,000 IU IL2/m.^{sup.2} body surface/day, the agent having a specific activity of 15.times.10.^{sup.6} IU/mg protein.

53. The method of claim 52, wherein the subject is selected from the group consisting of normal subjects and subjects afflicted with a condition associated with a viral, bacterial, fungal, and parasitic microorganism, a congenital and acquired immunodeficiency, and a malignancy.

54. The method of claim 53, wherein the subject is an HIV seropositive human, and the agent is administered, applied, self-administered, or self-applied in an amount and under conditions which avoid increasing the count of circulating microorganisms.

55. A method of administering or applying to a subject an agent selected from the group consisting of natural and recombinant IL-2, pharmaceutically acceptable fusion proteins of natural and recombinant IL-2, PEG-IL2 natural and recombinant, lipid-conjugated natural and recombinant IL-2, therapeutic agent-linked natural and recombinant IL-2, reduced natural and recombinant IL-2, glycosylated t in a IL-2, non-glycosylated natural and recombinant IL-2, and mixtures thereof, comprising the administration, application, self-administration, or self-application for a period greater than three months of a therapeutic product comprising the agent, which when administered or applied to a subject releases an amount of the agent over a pre-determined period of time effective to release about 100,000 to about 500,000 IU IL-2/m.^{sup.2} body surface/day or equivalent to about 100,000 to about 500,000 IU IL-2/m.^{sup.2} body surface/day, the agent having a specific activity of 15.times.10.^{sup.6} IU/mg protein.

56. The method of claim 55, wherein the product further comprises an ingredient selected from the group consisting of carriers, diluents, buffers, salt forming acids and bases, perfumes, colorants, emollients, adjuvants, single or multiple enteric coatings, copolymers, microporous or semi-permeable membranes, enzyme inhibitors, mucoadhesives, chelating agents, particulate systems, viral envelope proteins, liposomes and other micelles, emulsifiers, lipoproteins and other fatty acid

derivatives, surfactants, bile salts, hydrophilic, neutral, and hydrophobic polymers and co-polymers, hydrogels, biodegradable polymers and co polymers, and anti-inflammatories, an additional bioactive agent selected from the group consisting of additional lymphokines or cytokines, and fusion proteins of the lymphokines or cytokines, anti-inflammatories, anti-bacterial, anti-viral, anti-fungal, anti-parasitic, anti-metabolic, anti-inflammatory, vasoactive, anti-neoplastic, bronchodilating, local anesthetic, immunomodulating, growth promoting and regenerating agents, enzymatic, hormonal agents, neurotransmitters, and cell receptor proteins and ligands.

57. The method of claim 55, wherein the subject is selected from the group consisting of normal subjects and subjects afflicted with a condition associated with a viral, bacterial, fungal, and parasitic microorganism, a congenital and acquired immunodeficiency, and a malignancy.

58. The method of claim 57, wherein the subject is an HIV seropositive human, and the agent is administered, applied, self-administered, or self-applied in an amount and under conditions which avoid increasing the count of circulating microorganisms .

59. The method of claim 29, wherein the subject is a normal subject or a subject afflicted with a condition associated with a viral, bacterial, fungal, and parasitic microorganism, a congenital or acquire immunodeficiency, or a malignancy.

60. The method of claim 59, wherein the subject is an HIV seropositive human; and the composition is administered, applied, self-administered, or self-applied in an amount and under conditions which substantially avoid increasing the count of circulating microorganisms.

L8 ANSWER 14 OF 47 USPTFULL

2002:92231 Methods of therapy for HIV infection.

Sahner, David, Berkeley, CA, UNITED STATES

US 2002048748 A1 20020425

APPLICATION: US 2001-974470 A1 20011009 (9)

PRIORITY: US 2000-242090P 20001020 (60)

DOCUMENT TYPE: Utility; APPLICATION.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods for promoting immunologic control of human immunodeficiency virus (HIV) in an HIV-infected subject are provided. The methods comprise administering to the subject highly active antiretroviral therapy (HAART) for at least one cycle of an intermittent dosing regimen in combination with administration of a pharmaceutical composition comprising a therapeutically effective amount of interleukin-2 (IL-2) or variant thereof. The combination of daily or intermittent administration of IL-2 (or variant thereof) and intermittent HAART promotes immunologic control of viral replication in the absence of HAART, thereby prolonging the length of time a patient may discontinue HAART before viral rebound necessitates further administration of HAART. Administration of IL-2 therapy in combination with an intermittent HAART dosing regimen provides an effective method for treating a subject infected with HIV.

CLM What is claimed is:

1. A method of promoting immunologic control of human immunodeficiency virus (HIV) in an HIV-infected subject, said method comprising administering to said subject highly active antiretroviral therapy (HAART) for at least

one cycle of an intermittent dosing regimen in combination with administration of a pharmaceutical composition comprising a therapeutically effective amount of interleukin-2 (IL-2) or variant thereof, wherein said administration provides a baseline level of said IL-2 within said subject.

2. The method of claim 1, wherein said HAART comprises daily administration of at least three antiretroviral agents, wherein a therapeutically effective amount of each of said antiretroviral agents is administered.

3. The method of claim 2, wherein said antiretroviral agents are selected from the group consisting of reverse transcriptase inhibitors and protease inhibitors.

4. The method of claim 3, wherein said reverse transcriptase inhibitors are selected from the group consisting of dideoxyinosine (ddI), zidovudine (AZT), zalcitabine (ddC), lamivudine (3TC), stavudine (D4T), abacavir, delavirdine, efavirenz, and nevirapine.

5. The method of claim 3, wherein said protease inhibitors are selected from the group consisting of Indinavir (IDV), Amprenavir, saquinavir, ritonavir, ABT-378, nelfinavir, and GW141.

6. The method of claim 1, wherein said intermittent dosing regimen for HAART comprises administering HAART to said subject until plasma viral RNA is undetectable in said subject, and then discontinuing administration of said HAART until plasma viral RNA reaches an acceptable threshold level in said subject.

7. The method of claim 6, wherein said plasma viral RNA is undetectable in said subject for at least about one month prior to discontinuing HAART, and wherein said acceptable threshold level of said plasma viral RNA is about 10,000 molecules/ml at two consecutive measurements taken about one week apart.

8. The method of claim 1, wherein said IL-2 or variant thereof is administered subcutaneously.

9. The method of claim 1, wherein said IL-2 or variant thereof is administered daily.

10. The method of claim 9, wherein said therapeutically effective amount of said IL-2 or variant thereof is in the range from about 0.6 mIU/M.sup.2 to about 3.5 mIU/m.sup.2.

11. The method of claim 10, wherein said therapeutically effective amount of said IL-2 or variant thereof is in the range from about 0.7 mIU/m.sup.2 to about 3 mIU/m.sup.2

12. The method of claim 11, wherein said therapeutically effective amount of said IL-2 or variant thereof is about 1.20 mIU/m.sup.2.

13. The method of claim 1, wherein said IL-2 or variant thereof is administered intermittently.

14. The method of claim 1, wherein said pharmaceutical composition comprising IL-2 or variant thereof is selected from the group consisting of a stabilized monomeric IL-2

pharmaceutical composition, a multimeric IL-2 composition, a stabilized lyophilized IL-2 pharmaceutical composition, and a stabilized spray-dried IL-2 pharmaceutical composition.

15. The method of claim 14, wherein said IL-2 is recombinantly produced IL-2 having an amino acid sequence for human IL-2 or variant thereof.

16. The method of claim 15, wherein said variant thereof has an amino acid sequence having at least about 70% sequence identity to the amino acid sequence for said human IL-2.

17. A method of treating a subject infected with human immunodeficiency virus (HIV), said method comprising administering to said subject highly active antiretroviral therapy (HAART) for at least one cycle of an intermittent dosing regimen in combination with administration of a pharmaceutical composition comprising a therapeutically effective amount of interleukin-2 (IL-2) or variant thereof, wherein said administration provides a baseline level of said IL-2 within said subject.

18. The method of claim 17, wherein said HAART comprises daily administration of at least three antiretroviral agents, wherein a therapeutically effective amount of each of said antiretroviral agents is administered.

19. The method of claim 18, wherein said antiretroviral agents are selected from the group consisting of reverse transcriptase inhibitors and protease inhibitors.

20. The method of claim 19, wherein said reverse transcriptase inhibitors are selected from the group consisting of dideoxyinosine (ddI), zidovudine (AZT), zalcitabine (ddC), lamivudine (3TC), stavudine (D4T), abacavir, delavirdine, efavirenz, and nevirapine.

21. The method of claim 19, wherein said protease inhibitors are selected from the group consisting of Indinavir (IDV), Amprenavir, saquinavir, ritonavir, ABT-378, nelfinavir, and GW141.

22. The method of claim 17, wherein said intermittent dosing regimen for HAART comprises administering HAART to said subject until plasma viral RNA is undetectable in said subject, and then discontinuing administration of said HAART until plasma viral RNA reaches an acceptable threshold level in said subject.

23. The method of claim 22, wherein said plasma viral RNA is undetectable in said subject for at least about one month prior to discontinuing HAART, and wherein said acceptable threshold level of said plasma viral RNA is about 10,000 molecules/ml at two consecutive measurements taken about one week apart.

24. The method of claim 17, wherein said IL-2 or variant thereof is administered subcutaneously.

25. The method of claim 17, wherein said IL-2 or variant thereof is administered daily.

26. The method of claim 25, wherein said therapeutically effective amount of said IL-2 or variant thereof is in the

range from about 0.6 mIU/m.sup.2 to about 3.5 mIU/m.sup.2.

27. The method of claim 26, wherein said therapeutically effective amount of IL-2 or variant thereof is in the range from about 0.7 mIU/m.sup.2 to about 3 mIU/m.sup.2.

28. The method of claim 27, wherein said therapeutically effective amount of said IL-2 or variant thereof is about 1.20 mIU/m.sup.2.

29. The method of claim 17, wherein said IL-2 or variant thereof is administered intermittently.

30. The method of claim 17 wherein said pharmaceutical composition comprising IL-2 or variant thereof is selected from the group consisting of a stabilized monomeric IL-2 pharmaceutical composition, a multimeric IL-2 composition, a stabilized lyophilized IL-2 pharmaceutical composition, and a stabilized spray-dried IL-2 pharmaceutical composition.

31. The method of claim 30, wherein said IL-2 is recombinantly produced IL-2 having an amino acid sequence for human IL-2 or variant thereof.

32. The method of claim 31, wherein said variant thereof has an amino acid sequence having at least about 70% sequence identity to the amino acid sequence for said human IL-2.

33. A method of treating a subject infected with human immunodeficiency virus (HIV), said method comprising administering to said subject highly active antiretroviral therapy (HAART) for at least one cycle of an intermittent dosing regimen in combination with interleukin-2 (IL-2) therapy, wherein said IL-2 therapy comprises administering a pharmaceutical composition comprising a therapeutically effective amount of IL-2 or variant thereof throughout each cycle of said intermittent dosing regimen of HAART, wherein said administration provides a baseline level of said IL-2 within said subject, and wherein said intermittent dosing regimen for HAART comprises administering HAART to said subject until plasma viral RNA is undetectable in said subject for at least about one month prior to discontinuing HAART, and then discontinuing administration of said HAART until plasma viral RNA reaches at least about 10,000 molecules/ml at two consecutive measurements taken about one week apart.

34. The method of claim 33, wherein said IL-2 or variant thereof is administered daily by subcutaneous injection.

35. The method of claim 34, wherein said therapeutically effective amount of said IL-2 or variant thereof is in the range from about 0.2 mIU/m.sup.2 to about 5 mIU/m.sup.2.

36. The method of claim 35, wherein said therapeutically effective amount of IL-2 or variant thereof is in the range from about 0.5 mIU/m.sup.2 to about 2 mIU/m.sup.2.

37. The method of claim 36, wherein said therapeutically effective amount of said IL-2 or variant thereof is about 1.20 mIU/m.sup.2.

L8 ANSWER 22 OF 47 USPATFULL

2001:25423 Immunologic enhancement with intermittent interleukin-2 therapy.

Lane, H. Clifford, Bethesda, MD, United States

Kovacs, Joseph A., Potomac, MD, United States

Fauci, Anthony S., Washington, DC, United States

The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. corporation)

US 6190656 B1 20010220

APPLICATION: US 1997-922218 19970902 (8)

DOCUMENT TYPE: Utility; Granted.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for activating a mammalian immune system entails a series of IL-2 administrations that are effected intermittently over an extended period. Each administration of IL-2 is sufficient to allow spontaneous DNA synthesis in peripheral blood or lymph node cells of the patient to increase and peak, and each subsequent administration follows the preceding administration in the series by a period of time that is sufficient to allow IL-2 receptor expression in peripheral or lymph node blood of the patient to increase, peak and then decrease to 50% of peak value. This intermittent IL-2 therapy can be combined with another therapy which targets a specific disease state, such as an anti-retroviral therapy comprising, for example, the administration of AZT, ddI or interferon alpha. In addition, IL-2 administration can be employed to facilitate in situ transduction of T cells in the context of gene therapy. By this approach the cells are first activated in vivo via the aforementioned IL-2 therapy, and transduction then is effected by delivering a genetically engineered retroviral vector directly to the patient.

CLM What is claimed is:

1. A method for administration of interleukin-2 (IL-2) to increase immune function in a human subject, comprising: (a) administering an amount of IL-2 to a human subject in a first administration in an amount that is sufficient to increase the CD4 count in the subject as compared with the count prior to IL-2 administration, wherein the administration of IL-2 is continuous over a period of time that is sufficient to allow spontaneous DNA synthesis in peripheral blood or lymph node cells of the subject to increase and peak; (b) measuring the DNA synthesis in cells obtained from the subject during the administration period, wherein a time period of an increase or peak in DNA synthesis is indicative of an optimal duration of interleukin-2 (IL-2) administration; (c) administering a subsequent amount of IL-2 to the subject that is sufficient to increase the CD4 count in the subject as compared to the count prior to IL-2 administration, wherein the subsequent administration of IL-2 is continuous over a period of time that is sufficient to allow spontaneous DNA synthesis in peripheral blood or lymph node cells of the subject to increase and peak, and wherein the subsequent administration of IL-2 follows the first administration of IL-2 by a period of time that is sufficient to allow IL-2 receptor expression in peripheral blood or lymph node cells of the subject to increase as compared to the level of expression prior to IL-2 administration, peak then decrease to 50% of peak value; and (d) measuring the DNA synthesis in cells obtained from the subject during the subsequent administration, wherein a time period of an increase or

peak in DNA synthesis is indicative of an optimal duration of IL-2 administration; and (e) discontinuing administration of the subsequent amount of IL-2 administration at about the time of peak in DNA synthesis.

2. The method of claim 1, wherein IL-2 is administered in the first administration for a period of time from about one day to about 14 days and the subsequent administration of IL-2 begins at least 4 weeks after the end of the first administration of IL-2.

3. The method of claim 2, wherein the IL-2 is administered for about 5 days.

4. The method of claim 1, wherein the IL-2 is administered at a dosage of from 1.8 to 24 MU/day.

5. The method of claim 1, wherein the subject is an HIV-infected subject.

6. The method of claim 1, wherein the IL-2 administration is effected by continuous infusion.

7. The method of claim 1, wherein the IL-2 administration is effected by a series of subcutaneous injections.

8. The method of claim 7, wherein the IL-2 administration is effected by from 1-3 subcutaneous injections per day.

9. The method of claim 1, wherein IL-2 is administered for a period of time from about one day to about 14 days.

10. A method of activating the immune system of a subject, comprising: administering to the subject an amount of IL-2 sufficient to increase a level of helper/inducer T-cell function in the subject, wherein the IL-2 is administered in a series of successive continuous administrations, wherein each of the continuous administrations extend over a period of from 1 day to 2 weeks, and successive administrations are separated by a period of time of at least 4 weeks, wherein a duration of the continuous infusion is determined by measuring an increase in lymphocyte formation, and discontinuing administration of the IL-2 after a peak of lymphocyte formation has been detected.

11. The method of claim 10, wherein the peak of lymphocyte formation is determined by measuring lymphocyte blast formation.

12. The method of claim 10, wherein the peak of lymphocyte formation is determined by measuring DNA synthesis.

13. The method of claim 10, wherein the subject is infected with the human immunodeficiency virus.

14. A method of stimulating an immune response in a subject, comprising: administering to the subject a therapeutically sufficient dose of IL-2 for a sufficient period of time to stimulate an increase in a CD4 count of the subject compared to prior to administration of the IL-2, wherein the sufficient period of time is determined by identifying peak activation of the immune system by evaluating a parameter of T cell proliferation, and discontinuing administration of the IL-2 when or

after it is determined that peak activation has already occurred.

15. The method of claim 14, wherein peak activation of the immune system is determined by measuring lymphocyte blast formation.

16. The method of claim 15, wherein peak activation of the immune system is determined by measuring DNA synthesis in peripheral blood or lymph node cells of the subject.

17. The method of claim 14, further comprising repeatedly administering the therapeutically sufficient dose of IL-2 to the subject after a sufficient period of time for the subject's immune system to pass through a refractory period of relative resistance to stimulation with IL2.

18. The method of claim 17, further comprising determining that the subject's immune system has passed through the refractory period by determining that IL-2 receptor expression in peripheral blood or lymph node cells of the subject have decreased at least 50% from a peak value of IL-2 receptor expression during IL-2 administration.

L6 ANSWER 189 OF 198 USPATFULL

89:90683 Treatment of infections with lymphokines.

Chong, Kong-Teck, Union City, CA, United States

Cetus Corporation, Emeryville, CA, United States (U.S. corporation)

US 4879111 19891107

APPLICATION: US 1986-853122 19860417 (6)

DOCUMENT TYPE: Utility; Granted.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Infections in mammalian hosts may be treated therapeutically or prophylactically with an effective amount of at least one lymphokine before or after host infection, the amount being sufficient to achieve at least 50% protection of the host. Preferably, the lymphokine is IL-2 or a combination of TNF and IL-2 or TNF and IFN-.gamma.. Also, preferably the infection is bacterial and is being treated prophylactically. The combination of TNF and IL-2 or TNF and IFN-.gamma. is administered in synergistically effective amounts.

CLM What is claimed is:

1. A method for prophylactic or therapeutic treatment of bacterial infections in mammalian hosts comprising administering an effective amount of tumor necrosis factor (TNF) from a mammalian species, to the host, before or after infection of the host, wherein the amount of TNF is a sufficient dose to achieve at least 50% protection of the host.

2. The method of claim 1 wherein the TNF is from a human source.

3. The method of claim 2 wherein the TNF is recombinant and the treatment is prophylactic.

4. The method of claim 3 wherein the TNF is microbially produced.

5. The method of claim 4 wherein the TNF has its first eight amino acid residues deleted.

6. The method of claim 1 wherein the amount of TNF is a sufficient dose to achieve at least 70% protection of the host.

7. The method of claim 1 wherein the bacterial infection is a Gram-negative infection.

8. The method of claim 1 wherein the TNF is in admixture with a pharmaceutically acceptable carrier medium prior to administration.
9. A method for prophylactic or therapeutic treatment of bacterial infections in mammalian hosts comprising administering an effective amount of tumor necrosis factor (TNF) and interleukin-2 (IL-2), both from a mammalian species, to the host, before or after infection of the host, wherein the amount of TNF and IL-2 is a sufficient dose to achieve at least 50% protection of the host.
10. The method of claim 9 wherein the IL-2 and TNF are from a human source, the amount of IL-2 employed is 15,000-30,000 units and the amount of TNF employed is 0.01-0.02 micrograms per ml.
11. A method for prophylactic or therapeutic treatment of bacterial infections in mammalian hosts comprising administering an effective amount of tumor necrosis factor (TNF) and interferon-gamma (IFN-.gamma.), both from a mammalian species, to the host, before or after infection of the host, wherein the amount of TNF and IFN-.gamma. is a sufficient dose to achieve at least 50% protection of the host.
12. The method of claim 11 wherein the TNF and IFN-.gamma. are from a human source.
13. A method for prophylactic or therapeutic treatment of bacterial infections in human host comprising administering an effective amount of recombinant microbial produced human TNF to said host before or after the infection, wherein said amount of TNF is a sufficient dose to achieve at least 50% protection of said host.
14. A method for prophylactic or therapeutic treatment of gram negative bacterial infections in human host comprising administering an effective amount of recombinant microbial produced human TNF to said host before or after the infection, wherein said amount of TNF is a sufficient dose to achieve at least 50% protection of said host.
15. The method of claim 13, wherein said TNF is a mutein of TNF that lacks the first eight amino acids at the amino terminal end.
16. The method of claim 14, wherein said TNF is a mutein of TNF that lacks the first eight amino acids at the amino terminal end.

L12 ANSWER 39 OF 84 MEDLINE

90193650 Document Number: 90193650. PubMed ID: 2315671.
Interleukin-2. Smith K A. (Darmouth Medical
School.) SCIENTIFIC AMERICAN, (1990 Mar) 262 (3) 50-7. Journal code:
0404400. ISSN: 0036-8733. Pub. country: United States. Language: English.

L12 ANSWER 42 OF 84 MEDLINE

89369767 Document Number: 89369767. PubMed ID: 2672465.
Interleukin 2: prototype for a new generation of
immunoactive pharmaceuticals. Ciardelli T; Smith K A. TRENDS IN
PHARMACOLOGICAL SCIENCES, (1989 Jun) 10 (6) 239-43. Ref: 20. Journal
code: 7906158. ISSN: 0165-6147. Pub. country: ENGLAND: United Kingdom.
Language: English.

AB Molecular biological techniques have revealed the interleukin-
2 receptor to be a dimer composed of one alpha-subunit and one
beta-subunit which interact noncovalently in a cooperative manner.
Site-directed mutagenesis, in conjunction with structural analysis, is
beginning to clarify the relationship between structural components of the
receptor and their function, and Thomas Ciardelli and Kendall Smith
explain why this is bringing drug developers closer to the design of
IL-2 agonists and antagonists.

L12 ANSWER 28 OF 84 MEDLINE

92287427 Document Number: 92287427. PubMed ID: 1368227. Rational
immunotherapy with interleukin 2. Kaplan G; Cohn Z A;
Smith K A. (Laboratory of Cellular Physiology & Immunology,
Rockefeller University, New York, NY 10021.) BIO/TECHNOLOGY, (1992 Feb)
10 (2) 157-62. Ref: 44. Journal code: 8309273. ISSN: 0733-222X. Pub.
country: United States. Language: English.

AB Interleukin 2 (IL-2), a T
lymphocyte product released upon antigen stimulation, has been used for
cancer therapy in high doses for more than five years. More recently, its
potential as a stimulant of cell-mediated immunity in infectious diseases,
particularly those caused by intracellular microbes, has become
appreciated. Drawing on the extensive information available as to the
structure, cellular and molecular effects of IL-2,
this review focuses on its use in patients with lepromatous leprosy and
AIDS in low, physiologic doses. The data indicate that IL-
2 is effective in stimulating cell-mediated immunity without
systemic toxicity.

L12 ANSWER 24 OF 84 MEDLINE

93147738 Document Number: 93147738. PubMed ID: 8093894. Prolonged
immunostimulatory effect of low-dose polyethylene glycol
interleukin 2 in patients with human immunodeficiency
virus type 1 infection. Teppler H; Kaplan G; Smith K A; Montana
A L; Meyn P; Cohn Z A. (Laboratory of Cellular Physiology and Immunology,
Rockefeller University, New York, New York 10021.) JOURNAL OF
EXPERIMENTAL MEDICINE, (1993 Feb 1) 177 (2) 483-92. Journal code:
2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB 13 patients with human immunodeficiency virus type 1 infection class
II-IV, but without opportunistic infection or neoplasm, received 6
micrograms (3.6 x 10⁴) IU of polyethylene glycol recombinant human
interleukin 2 (PEG IL-2)
intradermally twice a week for 4 mo were then followed for an additional 6
mo. Clinical, immunological, and viral parameters were monitored in the
patients, all of whom were taking zidovudine. The cutaneous administration
of PEG IL-2 resulted in an indurated zone resembling a
delayed-type hypersensitivity response of 26 +/- 1 mm diameter (676 mm²)
at 72-96 h after injection throughout the 4 mo of administration. This

dose, which was appreciably lower than in most previous trials, was not associated with local or systemic toxicity. No increase in the viral burden of circulating leukocytes or plasma occurred. A number of immunological functions were stimulated by this course of therapy. All patients demonstrated high levels of lymphokine-activated killer cell activity by cells freshly removed from the circulation and in the absence of in vitro exposure to IL-2. Natural killer cell activity was also enhanced. Limiting dilution analysis revealed an increase in the frequency of IL-2-responsive cells from abnormally low to levels above normal during the course of injections. In a subgroup of four patients with $> \text{ or } = 400 \text{ CD4}^+ \text{ T cells/microliter}$ at entry, there was a trend to sustained increases in $\text{CD4}^+ \text{ T cell}$ numbers. However, this increase did not reach statistical significance. This subset of patients also exhibited higher proliferative responses to phytohemagglutinin as mitogen. Several of these effects persisted for 3-6 mo after cessation of therapy. In conclusion, low-dose IL-2 regimens lead to sustained immune enhancement in the absence of toxicity. We suggest pursuit of this approach for further clinical trials both as prophylaxis and therapy.

L12 ANSWER 14 OF 84 MEDLINE

96413659 Document Number: 96413659. PubMed ID: 8816813. Rational interleukin 2 therapy for HIV positive individuals: daily low doses enhance immune function without toxicity. Jacobson E L; Pilaro F; Smith K A. (Department of Medicine, New York Hospital-Cornell Medical Center, NY 10021, USA.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Sep 17) 93 (19) 10405-10. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB When administered in high doses to HIV positive (HIV+) individuals, interleukin 2 (IL-2) causes extreme toxicity and markedly increases plasma HIV levels. Integration of the information from the structure-activity relationships of the IL-2 receptor interaction, the cellular distribution of the different classes of IL-2 receptors, and the pharmacokinetics of IL-2 provides for the rationale that low IL-2 doses should circumvent toxicity. Therefore, to identify a nontoxic, but effective and safe IL-2 treatment regimen that does not stimulate viral replication, doses of IL-2 from 62,500 to 250,000 IU/m²/day were administered subcutaneously for 6 months to 16 HIV+ individuals with 200-500 $\text{CD4}^+ \text{ T cells/mm}^3$. IL-2 was already detectable in the plasma of most HIV+ individuals even before therapy. Peak plasma IL-2 levels were near saturating for high affinity IL-2 receptors in 10 individuals who received the maximum nontoxic dose, which ranged from 187,500 to 250,000 IU/m²/day. During the 6 months of treatment at this dose range, plasma levels of proinflammatory cytokines remained undetectable, and plasma HIV RNA levels did not change significantly. However, delayed type hypersensitivity responses to common recall antigens were markedly augmented, and there were IL-2 dose-dependent increases in circulating Natural Killer cells, eosinophils, monocytes, and $\text{CD4}^+ \text{ T cells}$. Expanded clinical trials of low dose IL-2 are now warranted, especially in combination with effective antivirals to test for the prevention of immunodeficiency and the emergence of drug-resistant mutants and for the eradication of residual virions.

L12 ANSWER 23 OF 84 MEDLINE

93200498 Document Number: 93200498. PubMed ID: 8453090. Lowest dose interleukin-2 immunotherapy. Smith K A. (Department of Medicine, Dartmouth Medical School, Hanover, NH 03755-3833.

) BLOOD, (1993 Mar 15) 81 (6) 1414-23. Ref: 106. Journal code: 7603509.
ISSN: 0006-4971. Pub. country: United States. Language: English.

L12 ANSWER 5 OF 84 MEDLINE

2001283427 Document Number: 20700681. PubMed ID: 11366819. IL-2 low dose and treatment interruption: interview with Kendall A. Smith. Interview by John S. James. Smith K A. AIDS TREATMENT NEWS, (1999 Oct 15) (No 329) 1-6. Journal code: 8809835. ISSN: 1052-4207. Pub. country: United States. Language: English.

AB In an interview, Kendall A. Smith, M.D., whose laboratory identified the IL-2 molecule and the IL-2 receptor, discusses a current study on administering low, daily doses of IL-2 to HIV patients who are also on HAART. One purpose of the study is to see if IL-2 increases the recovery of CD4 cells over an extended period. The second purpose is to see if a patient's immune system might be able to control the virus when HAART is interrupted, but IL-2 treatment is continued. The study results are described. Dr. Smith also discusses the history of IL-2 and other trials currently studying IL-2.

L12 ANSWER 10 OF 84 MEDLINE

1998118735 Document Number: 98118735. PubMed ID: 9457409. Rational interleukin-2 therapy. Smith K A. (Immunology Program, Graduate School of Medical Sciences, Cornell University, USA.) CANCER JOURNAL FROM SCIENTIFIC AMERICAN, (1997 Dec) 3 Suppl 1 S137-40. Journal code: 9513568. ISSN: 1081-4442. Pub. country: United States. Language: English.

AB The administration of cytokines that augment the function of the immune system can be accomplished safely and without toxicity, provided a rational approach is used. Such a therapeutic method should be based upon the principles of pharmacology and the structure-activity relationships of the cytokine-receptor interaction. Thus, the therapeutic index should be determined, and the goal should be to augment the function of the immune system in a variety of clinical situations, not necessarily focused on eradicating a particular disease process such as metastatic cancer that may or may not be influenced by the immune system.

L12 ANSWER 11 OF 84 MEDLINE

97244549 Document Number: 97244549. PubMed ID: 9121530. Interleukin-2 infusions in HIV-infected patients. Jacobson E L; Pilaro F; Smith K A. NEW ENGLAND JOURNAL OF MEDICINE, (1997 Apr 24) 336 (17) 1260-1. Journal code: 0255562. ISSN: 0028-4793. Pub. country: United States. Language: English.

L12 ANSWER 4 OF 84 MEDLINE

2001363436 Document Number: 21317671. PubMed ID: 11424974. Low-dose daily interleukin-2 immunotherapy: accelerating immune restoration and expanding HIV-specific T-cell immunity without toxicity. Smith K A. (Division of Immunology, Weill Medical College of Cornell University, New York, New York 10021, USA.. kasmith@med.cornell.edu) . AIDS, (2001 Feb) 15 Suppl 2 S28-35. Ref: 49. Journal code: 8710219. ISSN: 0269-9370. Pub. country: England: United Kingdom. Language: English.

AB There is now a great deal of interest in therapies focused on improving the function of the immune system in the treatment of individuals infected with the HIV. Although the antiviral drugs effectively suppress replication of the virus, they cannot cure the infection. Therefore, it now appears that both antivirals and immune system stimulants will be necessary to maximally suppress residual latent virus, thereby allowing the discontinuation of the antivirals without relapse of detectable plasma

virus. Interleukin-2 (IL-2) the first cytokine to be discovered at the molecular level has been used as a therapeutic in HIV infection, because it is critical for a normal functioning immune response. IL-2 is essential for the survival and proliferative expansion of antigen-activated T cells and natural killer (NK) cells, and also for promoting their differentiated functions of cytokine secretion and cytolysis. However, as IL-2 stimulates both the innate and acquired immune responses, when used as a therapeutic it can lead to severe toxicity when given in high doses. This review focuses on low dose, daily IL-2 therapy, used to accelerate the recovery of the immune system when viral replication is suppressed maximally with antivirals. In addition, the principles of the use of IL-2 to activate HIV-specific immune reactivity are discussed. At least two signals are required to promote the proliferative expansion and function of antiviral effector lymphocytes, HIV antigens and IL-2.

L12 ANSWER 3 OF 84 MEDLINE

2001543698 Document Number: 21474074. PubMed ID: 11590500. Low-dose daily subcutaneous interleukin-2 in combination with highly active antiretroviral therapy in HIV+ patients: a randomized controlled trial. Lalezari J P; Beal J A; Ruane P J; Cohen C J; Jacobson E L; Sundin D; Leong W P; Raffanti S P; Wheeler D A; Anderson R D; Keiser P; Schrader S R; Goodgame J C; Steinhart C R; Murphy R L; Wolin M J; Smith K A . (Quest Clinical Research, San Francisco, CA, USA.) HIV Clin Trials, (2000 Nov-Dec) 1 (3) 1-15. Journal code: 100936377. ISSN: 1528-4336. Pub. country: United States. Language: English.

AB PURPOSE: Previous studies with intermittent interleukin-2 (IL-2) therapy using intermediate and high levels of IL-2 have demonstrated significant increases in the CD4 + T cell count in HIV-infected patients. Intermittent regimens are amenable to outpatient use, but severe adverse events are frequently experienced with intermediate- and high-dose levels of IL-2. Therefore in this study, the effect of daily, subcutaneous low-dose IL-2 therapy on safety and immunological endpoints was investigated to determine whether immunological benefit could be achieved without toxicity in HIV-infected patients also receiving highly active antiretroviral therapy (HAART). METHOD: A total of 115 patients were enrolled in the trial. Fifty-six asymptomatic HIV-infected patients who had CD4 + T cell counts less than 300 cells/microL at screening and a stable HIV viral load received low-dose IL-2 (1.2 million IU [MIU]/m² beginning dose) once daily in conjunction with HAART (IL-2 group). Fifty-nine patients received HAART alone (control group). RESULTS: A dramatic effect of IL-2 on the natural killer (NK) cell population was observed with mean increases of 156 cells/microL in the IL-2 group compared to 19.93 cells/microL in the control group (p <.001). Additionally, IL-2-treated patients experienced a statistically significant increase in the mean percentage of CD4 + T cells (3.52% increase) when compared to control patients (1.33% increase) (p <.001). The expanded CD4 + T cell population was primarily of the naive phenotype, with mean increases of 4.53% for the IL-2 group and 0.31% for the control group (p <.001 for between-group difference). In addition, a higher proportion of IL-2-treated patients (67%) compared to control patients (33%) achieved increases of greater than 50% in the CD4+ T cell count (p =.08). Adverse events of grade 3 or grade 4 toxicity were infrequent in the current study and were substantially lower by comparison to those in studies of intermittent dose IL-2 therapy. Also, negligible changes in the HIV viral load from baseline to final measurement were observed in both groups. A trend toward a reduced number of modifications

of antiretroviral therapy was apparent in the IL-2 group when compared to control patients. CONCLUSION: Daily, low-dose subcutaneous IL-2 therapy in conjunction with HAART is safe and well tolerated and is effective in expanding lymphocyte cell types including NK cells and naive T cells in individuals who have <300 CD4+ T cells.

L12 ANSWER 2 OF 84 MEDLINE

2001543700 Document Number: 21474075. PubMed ID: 11590501. In vivo assessment of antiviral reactivity in chronic HIV infection. Smith K A; Jacobson E L; Sohn T; Warren D; Emert R; Giordano M. (Division of Immunology, Department of Medicine, Weill Medical College, Cornell University, New York 10021, USA.) HIV Clin Trials, (2000 Nov-Dec) 1 (3) 16-22. Journal code: 100936377. ISSN: 1528-4336. Pub. country: United States. Language: English.

AB PURPOSE AND METHOD: Chronic infection with HIV renders individuals incapable of mounting an effective host antiviral response, as defined by in vitro assays. Therefore, to determine whether antiviral reactivity could be detected in vivo, we interrupted effective antiviral treatment prospectively in nine chronically infected aviremic individuals. Low-dose interleukin-2 (IL-2) was administered before and after treatment interruption to compensate for any potential IL-2 production deficiency. In vivo antiviral reactivity was monitored subsequent to the interruption of antiviral therapy via viral and lymphocyte dynamics. The study was terminated when the plasma HIV RNA concentration reached a plateau, defined as four successive determinations that were <25% from the mean. RESULTS: Plasma viral relapse occurred in all participants; reaching a peak concentration within 2.5 weeks. However, over the subsequent 2 weeks viremia was reduced an order of magnitude coincident with a 2-fold lymphocytosis of the CD8 + T cell subset. A second treatment interruption resulted in attenuation of the peak and trough virus concentrations by <10-fold in 3 of 4 participants, while the CD8 + T cell concentrations remained elevated. CONCLUSION: These findings indicate that chronic HIV infection prior to successful antiviral therapy does not preclude host antiviral reactivity. In addition, in vivo antiviral reactivity as revealed by viral and lymphocyte dynamics after antiviral treatment interruption can be useful to monitor the efficacy of different therapies.

L12 ANSWER 1 OF 84 MEDLINE

2002004970 Document Number: 20535320. PubMed ID: 11082734. Restoration of immunity with interleukin-2 therapy. Smith K A ; Jacobson E L; Emert R; Giordano M; Kovacs E; Mumneh N; Pilaro F; Sohn T; Warren D. (Department of Medicine, Weill Medical College of Cornell University, New York, USA.) AIDS Read, (1999 Nov) 9 (8) 563-72. Ref: 64. Journal code: 9206753. ISSN: 1053-0894. Pub. country: United States. Language: English.

AB HIV replication can now be effectively suppressed using antiretroviral combination regimens. The search continues, however, for ways to restore the immune response and eliminate reservoirs of latent infection. Interleukin-2 (IL-2) may augment the immune response in HIV-infected persons. This article discusses the rationale for using IL-2 in those with HIV disease and reviews key trials of IL-2 treatment regimens.

L16 ANSWER 53 OF 67 MEDLINE

92330828 Document Number: 92330828. PubMed ID: 1628132. Cytokine-induced resistance to microbial infections in normal, immunosuppressed and bone marrow transplanted mice. Leshem B; Dekel R; Bercovier H; Tchakirov R; Polacheck I; Zakay-Rones Z; Schlesinger M; Kedar E. (Lautenberg Center for General and Tumor Immunology, Hebrew University-Hadassah Medical School,

Jerusalem, Israel.) BONE MARROW TRANSPLANTATION, (1992 Jun) 9 (6) 471-7.
Journal code: 8702459. ISSN: 0268-3369. Pub. country: ENGLAND: United
Kingdom. Language: English.

- AB We studied the efficacy of in vivo and in vitro treatments with IL-1, IL-2, IL-3, and GM-CSF in the protection against bacterial (*Salmonella typhimurium*), fungal (*Candida albicans*) and viral (influenza virus A/PR8) infections, of normal, sublethally irradiated and lethally irradiated, bone marrow (BM) reconstituted mice. In parallel, the cytokines were tested for their ability to potentiate hematopoietic activity in vitro and in vivo. We demonstrate that, under the experimental conditions employed, IL-1 had the best protective activity against the three micro-organisms in both normal and immunocompromised mice when administered in vivo. Administration of IL-2 led to increased resistance in normal but not in immunodeficient mice, whereas GM-CSF had no beneficial effects. In contrast, preincubation of BM cells in these cytokines, singly or combined, prior to transplantation to lethally irradiated mice, did not confer protection against subsequent infection, although it increased the number of BM derived CFU-GM in culture (except in the case of IL-2). Administration of IL-1 or GM-CSF to BM transplanted mice facilitated WBC recovery, whereas IL-2 delayed it. Collectively, the data suggest that IL-1, alone or combined with other cytokines, may be beneficial in the prevention or treatment of microbial infections in immunocompromised and BM transplanted patients. It can also be concluded that enhanced hematopoietic recovery may not always coincide with the development of resistance to micro-organisms.

L16 ANSWER 56 OF 67 MEDLINE

92221681 Document Number: 92221681. PubMed ID: 1373261. Multiple administration with interleukin-2 potentiates antigen-specific responses to subunit vaccination with bovine herpesvirus-1 glycoprotein IV. Hughes H P; Campos M; van Drunen Littel-van den Hurk S; Zamb T; Sordillo L M; Godson D; Babiuk L A. (Veterinary Infectious Disease Organization, Saskatoon, Saskatchewan, Canada.) VACCINE, (1992) 10 (4) 226-30. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

- AB Interleukin-2 has been described as an effective adjuvant for a number of antigens in different host species. Previously, we demonstrated the adjuvant activity of recombinant bovine IL-2 with a glycoprotein IV (gIV) subunit vaccine from bovine herpesvirus type-1 (BHV-1). In the present study, primary antibody responses were assessed in cattle immunized with either 2 or 50 micrograms of gIV, and treated with multiple doses of IL-2 or combinations of IL-2 and IFN-alpha or IL-2 and IFN-gamma. IL-2 was able to augment significantly antibody responses detected by either ELISA or virus neutralization. More significantly, IL-2 was able to enhance antibody titres in animals immunized with only 2 micrograms gIV to levels similar to those immunized with 50 micrograms gIV in the absence of IL-2. For optimal stimulation, multiple injections of IL-2 and Avridine had to be used in the formulation; other oil adjuvants or IL-2 alone could not induce a primary serum antibody response. Addition of IFN-alpha or IFN-gamma to the IL-2/gIV/Avridine formulation did not affect any of the immune parameters tested. As IFN-alpha is an effective immunoprophylactic agent for infectious bovine rhinotracheitis (IBR), combination vaccine-immunoprophylaxis may become feasible using IL-2 as a co-adjuvant. Thus, extremely low doses of antigen and only one immunization may be an effective vaccine given in combination with interferon prophylactic treatment.

L20 ANSWER 14 OF 14 MEDLINE

89002784 Document Number: 89002784. PubMed ID: 3048654. In vivo effects of recombinant human interleukin 2 on antitumor and antiviral natural immunity in induced or natural murine immunodeficiency states. Butler L D; Browne C P; Layman N K; Riedl P; Tang J; Marder P; DeLong D; Manetta J; Bobbitt L; Strnad J; +. (Department of Immunology Research, Lilly Research Laboratories, Indianapolis, Indiana 46285.) CANCER RESEARCH, (1988 Nov 1) 48 (21) 6081-9. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB We have examined the ability of in vivo treatment of mice with recombinant interleukin 2 (rIL-2) to affect natural immunity measured against tumor (YAC-1) or virally infected (herpes simplex type 1) target cells. rIL-2 treatment leads to significant increases in natural killer/lymphocyte-activated killer (NK/LAK) function and spleen cells recovered. This effect is dose dependent and strain related. The latter parameter correlated with the pretreatment NK activity level of the strain. The rIL-2 induced NK/LAK augmentation is also kinetically restricted as treatment must have occurred within 48-72 h of assay to be effective. The rIL-2 therapy effectively enhances both antitumor and antiviral NK/LAK activity and results in a noticeable increase in asialo-GM1-positive cells in the spleens of treated mice as well as a significant increase in IL-2 receptor expression as monitored by either cytometry or radioligand binding. In vivo treatment of mice with an antibody directed to the ASGM1 determinant effectively reduces the rIL-2 augmentation of both antitumor and antiviral activity even though this treatment does not affect the pretreatment level of antiviral activity. Various natural and induced immunodeficiency states (immunotherapy, irradiation, immunosuppressive drugs, cytoreductive drugs) have been examined for the ability of in vivo treatment with rIL-2 to enhance NK/LAK activity. In vivo rIL-2 administration is differentially effective in enhancing NK/LAK activity in these situations. Notably, in these induced immunodeficiency states, although NK/LAK activity is commonly enhanced, the number of spleen cells recovered often is only marginally affected. Thus, as expected, a limiting aspect in this use of a natural immunomodulator is the number of potentially responsive cells present in the immunodeficiency condition. In addition, correlations between rIL-2 effect, several of the immunodeficiency states, and vascular leak syndrome are briefly discussed.

L20 ANSWER 13 OF 14 MEDLINE

94132539 Document Number: 94132539. PubMed ID: 8301059. Pilot study of natural human interleukin-2 in patients with chronic hepatitis B. Immunomodulatory and antiviral effects. Tilg H; Vogel W; Tratkiewicz J; Aulitzky W E; Herold M; Gruber M; Geissler D; Umlauf F; Judmaier G; Schwulera U; +. (Department of Internal Medicine, Innsbruck University, Austria.) JOURNAL OF HEPATOLOGY, (1993 Sep) 19 (2) 259-67. Journal code: 8503886. ISSN: 0168-8278. Pub. country: Ireland. Language: English.

AB Ten patients with chronic hepatitis B received increasing doses of nIL-2 (30,000 U, 100,000 U, 300,000 U, 1.0 million U) subcutaneously in a phase I trial. Each dose was applied once per week over 3 weeks. Serum samples were taken before and 2, 12, 24, 48 and 72 h after the first application of each dose level. Serum concentrations of interleukin-1 (IL-1), IL-2, IL-6, interferon-alfa (IFN-alfa), IFN-gamma, tumor necrosis factor-alfa (TNF-alfa) and GM-CSF as well as the cytokine-dependent serum components neopterin, beta-2-microglobulin (B2M), C-reactive protein (CPR), soluble IL-2-receptor (sIL-2R) and 2'-5'-oligoadenylate synthetase (2-5 OA) were assayed using ELISAs and RIAs. None of the samples tested contained measurable cytokine levels other than IL-2. A low and non-toxic dose of 300,000 U nIL-2 was already biologically active with induction of neopterin, B2M and sIL-2R. Dose-dependent changes peaked 24-48 h after application. The same patients were then enrolled in a phase II trial.

Treatment in five of the patients was continued twice per week for 3 months with a biologically active dose of 300,000 U nIL-2 subcutaneously. Two of these patients as well as another five patients from the original group were treated with 1.0 million U nIL-2 subcutaneously, twice weekly for 3 months. Neither a biologically active but non-toxic dose of 300,000 U nIL-2, nor a toxic dose of 1.0 million U resulted in permanent clearance of hepatitis B early antigen (HBeAg). (ABSTRACT TRUNCATED AT 250 WORDS)

L20 ANSWER 12 OF 14 MEDLINE

94157475 Document Number: 94157475. PubMed ID: 8113740. Modulation of antiviral immune responses by exogenous cytokines: effects of tumour necrosis factor-alpha, interleukin-1 alpha, interleukin-2 and interferon-gamma on the immunogenicity of an inactivated rabies vaccine. Schijns V E; Claassen I J; Vermeulen A A; Horzinek M C; Osterhaus A D. (Department of Infectious Diseases and Immunology, Veterinary Faculty, University of Utrecht, The Netherlands.) JOURNAL OF GENERAL VIROLOGY, (1994 Jan) 75 (Pt 1) 55-63. Journal code: 0077340. ISSN: 0022-1317. Pub. country: ENGLAND: United Kingdom. Language: English.

AB In vivo administration of exogenous cytokines may influence elicited immune responses, and hence may change the efficacy of a vaccine. We investigated the effects of tumour necrosis factor-alpha (TNF-alpha), interleukin-1 alpha (IL-1 alpha), interleukin-2 (IL-2) and interferon-gamma (IFN-gamma) on the immune response elicited by inactivated rabies virus vaccine in a mouse model. Each of the cytokines increased virus-specific IgG responses after primary and after secondary immunization. A single dose of 1.3 ng TNF-alpha or IL-1 alpha, when injected shortly before vaccination, only marginally stimulated resistance to challenge infection (four- and seven-fold, respectively) without enhancing virus neutralizing antibody (VNAb) responses. In contrast, a single injection of 10(3) units of IFN-gamma or **five daily injections of 1.6 micrograms IL-2 increased vaccine dilutions protecting 50% of mice (PD50 values) 77- to 50-fold, respectively, with a concomitant enhancement of VNAb.** At a 1:10,000 dilution of a standard inactivated rabies vaccine preparation both IFN-gamma and IL-2 increased protective immunity without enhancing VNAb responses; in non-vaccinated animals this treatment had no effect on resistance to challenge. Combined administration of IFN-gamma and IL-2 synergistically enhanced VNAb responses. In contrast to the other cytokines tested, IFN-gamma preferentially stimulated virus-specific IgG2a production. It also augmented the vaccine-induced priming of rabies virus-specific splenocyte proliferation. These results document that certain cytokines alone or in combination are potent immunological adjuvants which may direct and modulate immunization-induced antiviral immune responses.

L20 ANSWER 8 OF 14 MEDLINE

96283750 Document Number: 96283750. PubMed ID: 8721559. Consensus symposium on combined antiviral therapy; overview of interferon and IL-2 combinations for the treatment of HIV infection. Sneller M C. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.) ANTIVIRAL RESEARCH, (1996 Jan) 29 (1) 105-9. Journal code: 8109699. ISSN: 0166-3542. Pub. country: Netherlands. Language: English.

AB Among the immunomodulatory cytokines that have been evaluated for the treatment of HIV disease, alpha-interferon and interleukin-2 (IL-2) have been the most extensively studied. Monotherapy with alpha-interferon is effective therapy for HIV-associated Kaposi's sarcoma (KS) in patients with CD4 counts > 150 cells/mm3. However, the doses necessary to achieve a significant anti-tumor effect are often poorly tolerated. Combination therapy with alpha-interferon and zidovudine is associated with

dose-limiting toxicities and an anti-tumor effect similar to that of higher dose alpha-interferon monotherapy. The combination of alpha-interferon and zidovudine can synergistically inhibit HIV replication in vitro; however, in vivo results suggest the anti-HIV effect of this combination is no greater than that seen with zidovudine monotherapy. Whether combination of interferon-alpha and other antiviral drugs will be useful in the treatment of HIV infection remains to be seen. Recent studies employing **intermittent courses of IL-2 combined with continuous antiretroviral therapy indicate that sustained rises in CD4 counts can be achieved. The ability of IL-2 therapy to result in a sustained rise in CD4 counts is critically dependent on the pre-treatment CD4 count.** The immunologic and clinical significance of these IL-2-induced increases in CD4 counts is unknown. Larger, controlled trials are currently underway to evaluate the role of intermittent IL-2 therapy in HIV infection.

L20 ANSWER 5 OF 14 MEDLINE

2000112500 Document Number: 20112500. PubMed ID: 10647974. A risk-benefit assessment of interleukin-2 as an adjunct to antiviral therapy in HIV infection. Piscitelli S C; Bhat N; Pau A. (Clinical Center Pharmacy Department, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA.. spisc@nih.gov) . DRUG SAFETY, (2000 Jan) 22 (1) 19-31. Ref: 58. Journal code: 9002928. ISSN: 0114-5916. Pub. country: New Zealand. Language: English.

AB Immunomodulation has become a major focus of HIV research in an effort to augment, boost or restore the patient's damaged immune system. Recombinant interleukin-2 is currently being studied in phase II/III trials in HIV-infected patients. Several clinical studies have demonstrated that intermittent regimens are associated with marked rises in CD4+ cell counts without an increase in viral load. Most of these studies employ 5 consecutive days of interleukin-2 therapy by continuous intravenous infusion or subcutaneous injection, repeated every 8 weeks. An alternative strategy is the daily administration of low doses of interleukin-2, but clinical experience with this regimen is limited. Interleukin-2 administration can adversely affect virtually every organ system, requiring aggressive supportive care. A variety of administration strategies and interventions are being evaluated to minimise toxicity. Currently, no clinical end-point data are available for interleukin-2 in HIV-infected patients. Until phase III studies are completed, interleukin-2 can be used in the research setting as an immunomodulator and adjunct to antiretroviral therapy. Its potential to activate latently infected cells and promote HIV eradication from reservoir sites is also an important area for further study. If clinical benefit can be demonstrated, interleukin-2 could be useful as an adjunct to antiretroviral therapy if adverse effects can be minimised and therapy can be given infrequently on an outpatient basis.

L20 ANSWER 4 OF 14 MEDLINE

2001231094 Document Number: 21219021. PubMed ID: 11319683. Efficacy of low-dose intermittent subcutaneous interleukin (IL)--2 in antiviral drug--experienced human immunodeficiency virus--infected persons with detectable virus load: a controlled study of 3 il-2 regimens with antiviral drug therapy. Tambussi G; Ghezzi S; Nozza S; Vallanti G; Magenta L; Guffanti M; Brambilla A; Vicenzi E; Carrera P; Racca S; Soldini L; Gianotti N; Murone M; Veglia F; Poli G; Lazzarin A. (Clinic of Infectious Diseases, San Raffaele Scientific Institute, 20137, Milan, Italy.. giuseppe.tambussi@hsr.it) . JOURNAL OF INFECTIOUS DISEASES, (2001 May 15) 183 (10) 1476-84. Journal code: 0413675. ISSN: 0022-1899. Pub. country:

United States. Language: English.

- AB To evaluate the safety and efficacy of 3 regimens of intermittent subcutaneous (sc) interleukin (IL)--2 in a phase 2 study, 61 antiviral drug-experienced human immunodeficiency virus (HIV)--positive patients were randomly assigned to one of the following study arms: antiretroviral therapy (ART) plus IL-2 (12 million IU [MIU] by continuous intravenous infusion, followed by 7.5 MIU twice a day, sc, every 8 weeks); ART plus IL-2 (7.5 MIU twice a day, sc, every 8 weeks); ART plus IL-2 (3 MIU twice a day, sc, every 4 weeks); or ART alone. **A significant increase of circulating CD4 cells was observed in IL-2--treated subjects**, compared with those given ART alone. Low doses of IL-2 were better tolerated. Despite the incomplete suppression of viral replication, IL-2 with ART did not increase either plasma viremia or cell-associated HIV DNA levels. Low doses of intermittent sc IL-2 induced a stable increase of peripheral CD4 cells that was indistinguishable from those associated with higher, less well-tolerated doses of IL-2.

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89264594 Document Number: 89264594. PubMed ID: 2786210.

Interleukin 2 acts as an adjuvant to increase the potency of inactivated rabies virus vaccine. Nunberg J H; Doyle M V; York S M; York C J. (Department of Microbial Genetics, Cetus Corporation, Emeryville, CA 94608.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1989 Jun) 86 (11) 4240-3. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

- AB Interleukin 2 (IL-2) occupies a central position in the cascade of events involved in the immune response. We were interested in determining whether IL-2 could function as an adjuvant to vaccination, to increase the immune response to vaccine immunogens. Using the National Institutes of Health test for rabies vaccine potency, we found that daily systemic administration of IL-2 in conjunction with inactivated rabies virus can increase the potency of vaccination in outbred mice at least 25-fold, as measured by survival following challenge with virulent rabies virus. Enhanced protection is not correlated with an increase in virus-neutralizing antibody titers, and we suggest that IL-2 acts to increase the cellular immune response to vaccination.

L22 ANSWER 31 OF 44 MEDLINE

92221677 Document Number: 92221677. PubMed ID: 1561827.

Liposome-formulated interleukin-2 as an adjuvant of recombinant HSV glycoprotein gD for the treatment of recurrent genital HSV-2 in guinea-pigs. Ho R J; Burke R L; Merigan T C. (Department of Medicine, Stanford University School of Medicine, CA 94305.) VACCINE, (1992) 10 (4) 209-13. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

- AB The use of interleukin-2 (IL-2) as an adjuvant to enhance an antigen-induced immunotherapeutic effect was investigated using guinea-pigs with established HSV-2 infection. Animals treated with four weekly doses of liposome-formulated IL-2 (2.7×10^5 U/kg-1 dose) overlapping two biweekly doses of an HSV-recombinant glycoprotein D (rgD) treatment demonstrated approximately 70% reduction in HSV-2 recurrent disease compared with placebo (p less than 0.005). Combination therapy rgD plus liposome-formulated IL-2 exhibited approximately 30% greater therapeutic effect than either agent alone (p less than 0.05). Liposome formulation of IL-2 was essential to elicit the adjuvant effect. Identical biweekly dosing or more frequent daily dosing of soluble IL-2 did not produce additional therapeutic effects, suggesting the role of liposome targeting to lymph nodes. Although rgD plus liposome-formulated IL-2 induced a marginal early antibody response to rgD, there was no significant increase in overall antibody response. Combination therapy increased the frequency of minimally positive HSV lymphoproliferative

response.

L22 ANSWER 23 OF 44 MEDLINE

95264752 Document Number: 95264752. PubMed ID: 7745993. Adjuvant effect of low-dose interleukin-2 on antibody response to influenza virus vaccination in healthy elderly subjects. Provinciali M; Di Stefano G; Colombo M; Della Croce F; Gandolfi M C; Daghetta L; Anichini M; Della Bitta R; Fabris N. (Immunology Center, INRCA Gerontology Research Department, Ancona, Italy.) MECHANISMS OF AGEING AND DEVELOPMENT, (1994 Dec 16) 77 (2) 75-82. Journal code: 0347227. ISSN: 0047-6374. Pub. country: Ireland. Language: English.

AB It is well known that immune efficiency is frequently deteriorated in elderly people. The age-diminished antibody response to T-cell dependent antigens, such as influenza virus antigens, may explain the low protection offered by influenza vaccination in the elderly population. To investigate the possibility of increasing the antibody response to influenza virus vaccinations, we have conducted a nursing home-based study on the efficacy of IL-2. Seventy-five institutionalized elderly subjects (82 +/- 8 years) were enrolled in the study in the course of winter season 1991-1992. Thirty-nine subjects were treated with three subcutaneous daily injections of interleukin-2 (IL-2, 1 x 10⁶ I.U./day) before vaccination and their antibody response was compared to that of 36 aged people receiving the vaccine only. An increased antibody response against influenza virus was present in vaccine plus IL-2 treated subjects (P < 0.001) but not in subjects treated with vaccine only. The number of protected subjects 45 days after vaccination was increased only in the IL-2-treated group (P = 0.045). The low-dose of IL-2 administered and the short-term treatment allowed a good tolerance to the IL-2 injection. In conclusion, the low-dose IL-2 treatment represents an effective means of inducing antibody response to influenza virus antigens in elderly subjects without appreciable toxicity.